New approach to the functionalization of δ-carboline derivatives

*S. Yu. Ryabova,[a] L. M. Alekseeva,[a] E. A. Lisitza,[a] A. S. Shashkov,[b] V. V. Chernyshev,[c] G. B. Tichomirova,[a] M. S. Goyzman,[a] and V. G. Granik[a]**

[a]*Russian Federation State Scientific Center "Scientific Research Institute of Organic Intermediates and Dyes", 1, building 4, Bol'shaya Sadovaya, 103787 Moscow, Russian Federation. Fax: +7 (095) 254 6574. E-mail: makar-cl@ropnet.ru*

[b]*N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 47 Leninsky prosp., 119991 Moscow, Russian Federation. Fax: +7 (095) 135 5328*

[c]*Department of Chemistry, M. V. Lomonosov Moscow State University, Leninskie Gory, 119899 Moscow, Russian Federation. Fax: +7 (095) 939 3654. E-mail: cher@biocryst.phys.msu.su*

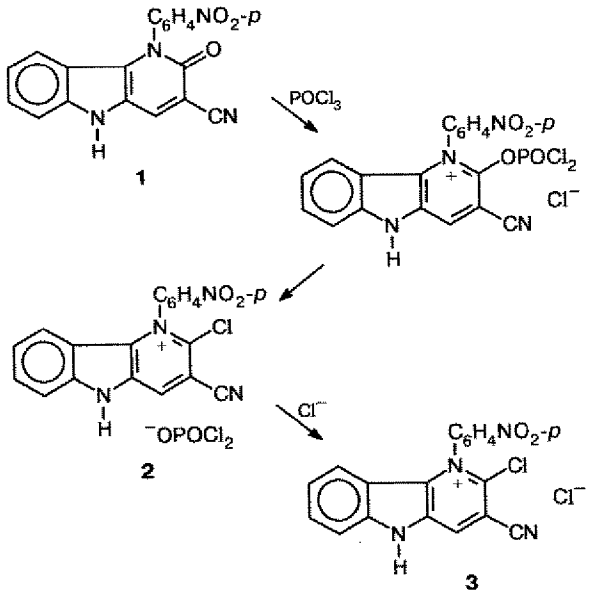
The possibility of transformation of 3-cyano-1-*p*-nitrophenyl-δ-carbolin-2-one into 2-amino-3-cyano-1-*p*-nitrophenyl-1*H*-pyrido[3,2-*b*]indole derivatives and 2-imino-3-cyano-1-*p*-nitrophenyl-5*H*-pyrido[3,2-*b*]indole derivatives (δ-carbolines) is demonstrated. Methylation of 1-*p*-nitrophenyl-2-piperidino-1*H*-δ-carboline followed by treatment with acetone in an alkaline medium yields 4-acetonyl-5-methyl-1,4-dihydro-5*H*-pyrido[3,2-*b*]indole derivative. The rearrangement of 2-arylimino-3-cyano-1-*p*-nitrophenyl-5*H*-pyrido[3,2-*b*]indoles into 2-(aryl)nitrophenylamino-3-cyano-5*H*-pyrido[3,2-*b*]indoles was accomplished on heating above the melting point or on treatment with potassium *tert*-butoxide. The structures of the resulting compounds were proved by ^{1}H and ^{13}C NMR spectroscopy and X-ray diffraction analysis.

Key words: δ-carboline, pyrido[3,2-*b*]indole, adduct with $POCl_3$, nucleophilic reagents, rearrangement, methylation, NMR, UV spectroscopy, X-ray diffraction analysis.

Fused heterocyclic systems containing indole and pyridine fragments arouse considerable interest.[1] Well-known medicines such as diazoline and dimebone (γ-carboline derivatives) and incazan (β-carboline derivative) are also substituted carbolines.[2] However, δ-carboline derivatives, which are somewhat less readily available, have not been adequately studied yet.[1] Recently,[3] we found that 3-*p*-nitrophenylaminoindole can be readily transformed into 3-cyano-1-*p*-nitrophenyl-5*H*-pyrido[3,2-*b*]indol-2-one (**1**), which is a convenient synthon for the synthesis of pyrido[3,2-*b*]indole (δ-carboline) derivatives. This paper deals with investigation of the methods of functionalization of δ-carboline **1**. The synthetic strategy chosen here is based on the known approach[4] to the activation of the amide fragment upon conversion of **1** upon the reaction with $POCl_3$. This type of activation of the amide function has been studied in detail for simple amides and lactams[5—7] but much less studied for more complicated representatives of these classes.[8—10]

It was found that heating δ-carboline **1** with $POCl_3$ gives an adduct, which was identified as compound **2** on the basis of published data[11,12] (Scheme 1). The reaction involved can be represented as initial *O*-acylation of **1** followed by an attack of the chloride anion on position 2. In the case where the reaction mixture contains an additional source of Cl^- anions, for example, triethylamine hydrochloride, a mixture of complexes **2** and **3** is apparently formed.[11,12]

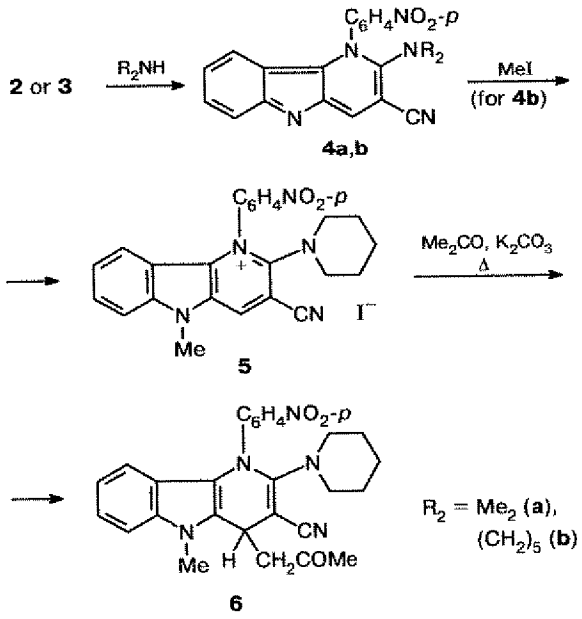
Scheme 1



Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya*, No. 8, pp. 1379—1385, August, 2001.

Although the positive charge of the cations of the complexes is efficiently delocalized, the reactions with nucleophiles are expected to proceed rather smoothly to give 2-substituted δ-carbolines. Indeed, the reactions of complex **2** or **3** with highly basic amines, *viz.*, dimethylamine and piperidine, occur without heating giving rise to 2-dimethylamino- and 2-piperidino-substituted 3-cyano-1-*p*-nitrophenyl-1*H*-pyrido[3,2-*b*]indoles (**4a,b**), whose structure follows unambiguously from the data of the ^{1}H NMR spectra. These compounds tend to undergo double bond migration and, although they are aromatic in accordance with the known principle of $(4n+2)$ π-electrons, the indole fragment in them is not aromatized and can be subjected to *N*-alkylation to give a 1-R-pyrido[3,2-*b*]indolium system. As indicated by our previous publications,[13,14] cations of this type should add carbanionic species at position 4 of the molecule. Indeed, on treatment with MeI, compound **4b** is readily converted into 3-cyano-5-methyl-1-*p*-nitrophenyl-2-piperidino-5*H*-pyrido[3,2-*b*]indolium iodide (**5**), which is converted into 4-acetonyl-3-cyano-5-methyl-1-*p*-nitrophenyl-2-piperidino-1,4-dihydropyrido[3,2-*b*]indole (**6**) on heating in acetone in the presence of potassium carbonate (Scheme 2).

Scheme 2



The high reactivity of complexes **2** or **3** toward nucleophilic reagents is also demonstrated by the fact that they readily react with weakly basic amines, *viz.*, aniline and *p*-chloroaniline to give 3-cyano-1-*p*-nitrophenyl-2-phenylimino- (**7a**) and 3-cyano-1-*p*-nitrophenyl-2-*p*-chlorophenylimino-1,2-dihydro-5*H*-pyrido-[3,2-*b*]indoles (**7b**) (Scheme 3). The imine structure of the compounds synthesized was confirmed by the data of ^{1}H NMR spectra (see Table 1), in particular, by the presence of singlet signals at δ ~11.5, corresponding to the indole NH protons. An important feature of the spectra of 2-imino-δ-carbolines **7a,b** is that the signals for the protons in position 9 are located in a rather high field (δ ~ 6 ppm), pointing to an anisotropic influence of the $C_6H_4NO_2$-group benzene ring, which is deflected from the plane of the tricyclic system. The imine structure of compounds **7a,b** is also confirmed by the fact that they are readily protonated at the imino-group nitrogen atom being thus converted into hydrochlorides **8a,b**. The ^{1}H NMR spectra of salts **8a** and **8b** are virtually identical. All the signals in the spectra of hydrochlorides are shifted downfield with respect to those in the spectra of the initial bases. The spectrum of hydrochloride **8b** measured in DMSO-d_6 is almost identical to the spectrum of base **7b** recorded in CF_3COOD, except that the spectrum of **8b** contains a singlet for N^+H at δ 9.56.

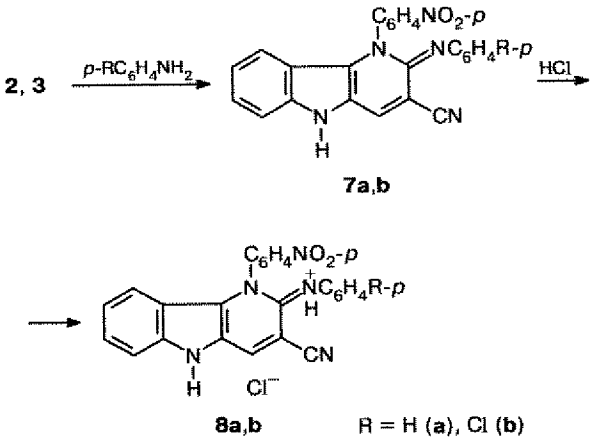
A rather interesting phenomenon is observed when 2-imino-δ-carbolines **7a,b** are heated above the melting

Table 1. ^{1}H NMR spectra of compounds **7a,b**, **9a,b**

Compound	δ				
	$C_6H_4NO_2$	C_6H_4-R-*p* (R = H, Cl)	H(4)	NH	H(6)—H(9)
7a	7.90, 8.50 (AA′XX′, 4 H, N(1)—$C_6H_4NO_2$)	6.68—7.13 (m, 5 H, C_6H_5)	8.26 (s, 1 H)	11.50 (br.s, 1 H)	5.92 (d[a], 1 H, H(9)); 6.80 (t[b], 1 H, H(8)); 7.30 (t[b], 1 H, H(7)); 7.47 (d[a], 1 H, H(6))
7b	7.89, 8.49 (AA′XX′, 4 H, N(1)—$C_6H_4NO_2$)	6.70, 7.14 (AA′XX′, 4 H, C_6H_4Cl)	8.29 (s, 1 H)	11.53 (br.s, 1 H)	5.93 (d[a], 1 H, H(9)); 6.80 (t[b], 1 H, H(8)); 7.31 (t[b], 1 H, H(7)); 7.48 (d[a], 1 H, H(6))
9a	6.89, 8.11 ((AA′XX′, 4 H, N(2)—$C_6H_4NO_2$)	7.20—7.46 (m, 5 H, C_6H_5)	8.58 (s, 1 H)	12.02 (br.s, 1 H)	8.13 (d[a], 1 H, H(9)); 7.66 (m, 2 H, H(6), H(7))[c]
9b	6.94, 8.11 (AA′XX′, 4 H, N(2)—$C_6H_4NO_2$)	7.28, 7.49 (AA′XX′, 4 H, C_6H_4Cl)	8.59 (s, 1 H)	12.11 (br.s, 1 H)	8.11 (d[a], 1 H, H(9)); 7.28 (t[b], 1 H, H(8)); 7.63 (t[b], 1 H, H(7)); 7.68 (d[a], 1 H, H(6))

[a] $J_{9,8} = J_{ortho} = 8.4$ Hz.
[b] $J_{7,8} = J_{7,6} = 8.4$ Hz; $J_{8,9} = J_{8,7} = 8.4$ Hz.
[c] The signal for H(8) falls in the 7.20—7.46 ppm region.

Scheme 3



point. In this case, both substances are irreversibly transformed into isomers; on the basis of spectral data, the isomers should be identified as the corresponding 3-cyano-2-diarylamino-5*H*-pyrido[3,2-*b*]indoles **9a,b** (Scheme 4). The ^{1}H NMR spectra of compounds **7a,b** and **9a,b** differ in the chemical shifts of like protons (the proton signals for the fused benzene ring were assigned based on the COSY spectrum). In the spectra of compounds **9a,b**, the signal of the H(9) proton is shifted downfield by more than 2 ppm. Attention is attracted by the great difference in the change of the chemical shifts of protons of the aryl substituents. Indeed, the signals of *p*-$NO_2C_6H_4$ in the spectrum of **9b** are shifted upfield by 0.95 (H(2), H(6)) and by 0.38 ppm (H(3), H(5)) with respect to those in the spectrum of **7b**, while the signals of *p*-ClC_6H_4 are displaced downfield by 0.58 and 0.35 ppm, respectively. Important information was gained from the ROESY spectra: the spectrum **7b** contains no correlation peaks corresponding to the coupling of protons of *p*-$NO_2C_6H_4$ and *p*-ClC_6H_4; conversely, in the spectrum of **9b**, this correlation is observed between the 6.94/7.49 and 6.94/7.28 ppm signals. This indicates that the aryl substituents in compounds **7a,b** are spatially separated, while in compounds **9a,b**, they are brought close in space. The differential NOE spectra of both types of isomers exhibit responses of signals of the protons in positions 4 and 6 upon pre-saturation of the N(5)H protons; this indicates unambiguously that the molecule contains an aromatic indole system. Finally, as has already been noted, the addition of acids to **7a,b** results in protonation at the exocyclic N atom. Compounds **9a,b**, unlike **7a,b**, cannot be protonated and form no hydrochlorides; the spectra of **9a,b**, recorded in CF_3COOD virtually do not differ in chemical shifts from the spectra recorded in DMSO-d_6. The data of UV spectra (Table 2) of carbolines **7a,b** recorded in the presence of an acid also imply protonation of these

Scheme 4

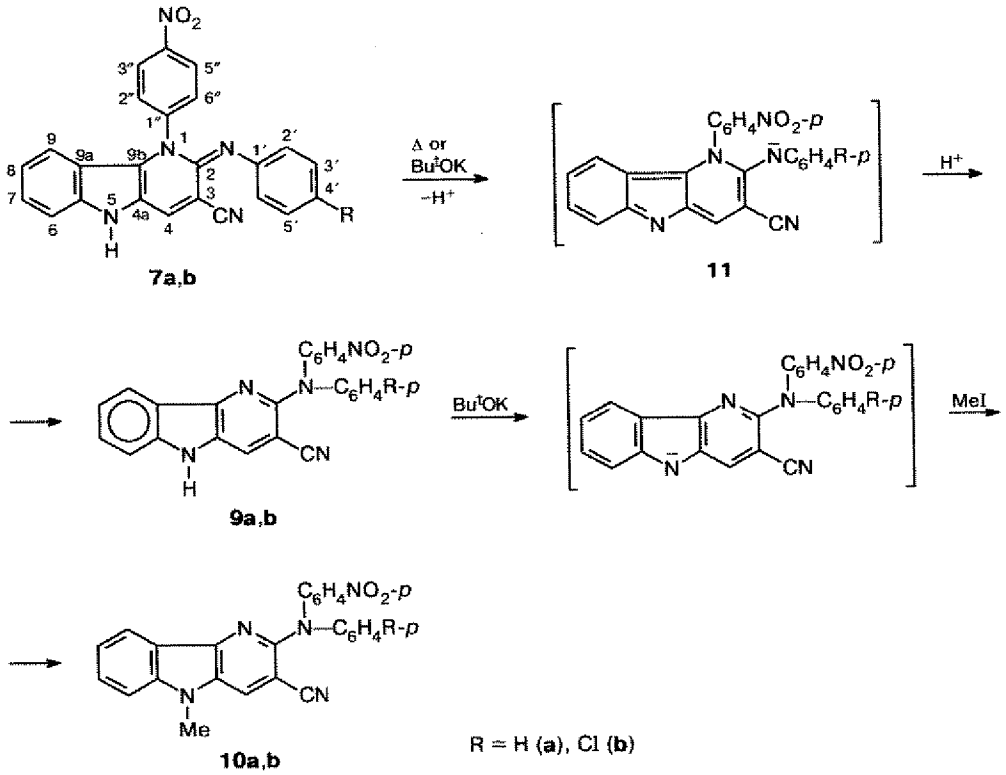


Table 2. Physicochemical properties of the compounds synthesized

Compound	M.p./°C (solvent)[a]	Yield (%) (method of synthesis)	MS, m/z (I_{rel} (%))	Molecular formula	Found / Calculated (%) C	H	N	Cl	UV, λ_{max}/nm (log ε) MeOH	MeOH + HCl
4a [b]	295—297 (DMF)	14	357 $[M]^+$ (100), 342$[M - Me]^+$ (51), 327 $[M - Me_2]^+$ (10), 311 $[M - NO_2]^+$ (14), 254 $[M - C_6H_4 - HCN]$ (10), 235 $[M - C_6H_4NO_2]^+$ (17), 194 $[M - Me - C_6H_4NO_2 - CN]^+$ (38)	$C_{20}H_{15}N_5O_2$	67.20 / 67.22	4.09 / 4.23	19.38 / 19.60	—	—	—
4b [b]	321 dec.	29	397 $[M]^+$ (100), 351 $[M - NO_2]^+$ (3), 275 $[M - C_6H_4NO_2]^+$ (6)	$C_{23}H_{19}N_5O_2$	69.58 / 69.51	5.11 / 4.82	17.36 / 17.62	—	—	—
5	311 dec. (Pr^iOH—acetone, 2 : 1)	91		$C_{24}H_{22}N_5IO_2$	—	—	12.88 / 12.99	—	—	—
6	214—216 (MeOH—dioxane, 4 : 1)	53	469 $[M]^+$ (7), 412 $[M - CH_2COMe]^+$ (100)	$C_{27}H_{27}N_5O_3$	69.71 / 69.06	6.00 / 5.80	14.86 / 14.92	—	—	—
7a [b]	205—206 (MeOH—acetone, 1 : 1)	14	405$[M]^+$ (83), 404$[M - H]^+$ (100), 358$[M - H - NO_2]^+$ (45)	$C_{24}H_{15}N_5O_2$	71.05 / 71.10	4.16 / 3.73	17.10 / 17.28	—	259 (4.37), 294 (4.14), 357 (4.11), 440 sh (3.74), 484 (3.85)	385 (4.21), 284 sh (4.17), 419 sh (4.07)
7b [b]	253 (MeOH—acetone, 1 : 1)	52	439 $[M]^+$ (100), 393 $[M - NO_2]^+$ (25), 358 $[M - NO_2 - Cl]^+$ (9)	$C_{24}H_{14}ClN_5O_2$	65.23 / 65.53	3.44 / 3.21	16.09 / 15.92	8.04 / 8.06	235 (4.42), 256 (4.38), 298 (4.15), 357 (4.13), 434—448 sh (3.76), 485 (3.87)	212 sh (4.52), 241 (4.35), 284 sh (4.13), 385 (4.18), 415 sh (4.01)
8a	266 (DMF—acetone, 1 : 4)	60	—	$C_{24}H_{16}ClN_5O_2$	65.18 / 65.24	3.79 / 3.65	15.64 / 15.85	7.81 / 8.02	—	—
8b	229—230 (MeOH—acetone, 1 : 9)	63	—	$C_{24}H_{15}Cl_2N_5O_2$	—	—	—	14.75 / 14.89	—	—
9a [c]	327—329 (H_2O—DMF, 1 : 4)	70 (*A*) 60 (*B*) 82 (*C*)	$[M]^+$ 405, 1206 [d] M = 405, 425	$C_{24}H_{15}N_5O_2$	—	—	—	—	256 (4.44), 295 (4.34), 351 sh (4.26), 379 (4.32)	256 (4.42), 296 (4.33), 351 sh (4.25), 380 (4.32)
9b [c]	196—199 (MeOH)	61	439 $[M]^+$ (100), 393 $[M - NO_2]^+$ (12)	$C_{24}H_{14}ClN_5O_2$	64.94 / 65.53	3.47 / 3.21	15.62 / 15.92	—	261 (4.43), 299 (4.37), 354 sh (4.26), 376 (4.30)	261 (4.41), 298 (4.36), 354 sh (4.25), 376 (4.29)
10a	260—260.5 (MeOH—acetone, 1 : 1)	58 (*A*) 88 (*B*)	419 $[M]^+$ (100), 373 $[M - NO_2]^+$ (27), 358 $[M - NO_2 - Me]^+$ (9)	$C_{25}H_{17}N_5O_2$	71.91 / 71.59	4.21 / 4.00	16.77 / 16.70	—	228 (4.45), 259 br (4.42), 295 (4.39), 356 sh (4.29), 377 (4.32)	228 (4.44), 262 br (4.41), 295 (4.39), 359 sh (4.29), 377 (4.32)

(*to be continued*)

Table 2 (*continue*)

Compound	M.p./°C (solvent)[a]	Yield (%) (method of synthesis)	MS, m/z (I_{rel} (%))	Molecular formula	Found / Calculated (%) C	H	N	Cl	UV, λ_{max}/nm (log ε) MeOH	MeOH + HCl
10b[c]	265.5—266 (MeOH—acetone, 1 : 2)	22 (*A*) 84 (*B*)	453 $[M]^+$ (100), 439 $[M - Me]^+$ (3), 407 $[M - NO_2]^+$ (11), 392 $[M - Me - NO_2]^+$ (4)	$C_{25}H_{16}ClN_5O_2$	66.38 / 66.15	3.59 / 3.55	14.98 / 15.43	7.38 / 7.81	264 (4.45), 298 (4.43), 359 sh (4.29), 378 (4.31)	265 (4.44), 299 (4.42), 357 sh (4.28), 379 (4.31)

[a] Solvent for crystallization.
[b] The yield of compound was calculated for δ-carbolin-2-one **1**.
[c] To record the UV spectrum, the compound was dissolved in DMSO and the solution was diluted with MeOH.
[d] High-resolution mass spectra were recorded on a Finnigan-Mat TSQ 700 instrument (triple quadrupole) with direct sample injection into the ion source.

compounds, whereas **9a,b** are not protonated under the same conditions. An important difference between the electronic spectra of the isomers under study is that the long-wavelength band of **7a,b** undergoes a strong bathochromic shift (by about 100 nm) compared to that of **9a,b**, indicating that the chromophore is much more extended in the former type of compound.

The HMBC spectra of both types of isomers contain identical correlation peaks. Comparison of the ^{13}C NMR spectra of compounds **7b** and **9b** shows that only the chemical shifts of carbon atoms located in immediate vicinity of the pyridine nucleus differ substantially (Table 3). Thus the signal of the C(9b) atom in compound **9b** is shifted downfield by 13.3 ppm, that of C(4a) is shifted by 9.7 ppm, that for C(3), by 7.9 ppm, and the signal of C(9a) is displaced by 5.9 ppm with respect to similar signals in the spectrum of **7b**. Conversely, the signal of C(4) is shifted 11.7 ppm upfield on

Table 3. ^{13}C NMR spectra of compounds **7a,b** and **9b**, **10b** and proton—carbon correlations in the HMBC spectrum

C atoms	δ			
	7a[a]	**7b**[b]	**9b**	**10b**[c]
2	146.8 (H(4))	147.5	149.4 (H(4))	149.4 (H(4))
3	94.8	94.8	102.7	102.7
4	137.1	137.3	125.6	124.4
4a	[d]	120.5	130.2	131.5 (Me)
5a	140.0 (H(7), H(9))	140.3	143.0 (H(7), H(9))	143.6 (H(9), H(7), Me)
6	112.8 (H(8))	112.9	112.5 (H(8))	110.5 (H(8))
7	127.6 (H(9))	127.8	129.9 (H(9))	130.0 (H(9))
8	119.9 (H(6))	119.9	120.5 (H(6))	120.7 (H(6))
9	120.2 (H(7))	120.3	121.2 (H(7))	121.2 (H(7))
9a	114.2 (H(6), H(8))	114.2	120.1 (H(8))	119.9 (H(6), H(8))
9b	130.0 (H(4))	130.1	143.4 (H(4))	142.6 (H(4))
1′[e]	149.4 (H(3′), H(5′))	148.7	142.6 (H(3′), H(5′))	142.6 (H(3′), H(5′))
2′6′[e]	121.4 (H(2′), H(6′), H(4′))	123.1	127.2 (H(2′), H(6′))	127.2 H(2′)) (H(6′)
3′5′[e]	128.5 (H(3′), H(5′))	128.3	129.9 (H(3′), H(5′))	129.8 (H(3′), H(5′))
4′[e]	121.6	125.1	127.2 (H(2′), H(6′))	127.2 H(2′), H(6′))
1″[f]	145.6 (H(3″), H(5″))	145.5	152.3 (H(3″), H(5″))	152.2 (H(3″), H(5″))
2″6″[f]	130.7 (H(2″), H(6″))	130.7	118.3 (H(2″), H(6″))	118.4 (H(2″), (H(6″))
3″5″[f]	125.5 (H(3″), H(5″))	125.6	125.4 (H(3″), H(5″))	125.4 (H(3″), H(5″))
4″[b]	147.4 (H(2″), H(6″))	147.5	140.6 (H(2″), H(3″), H(5″), H(6″))	140.6 (H(2″), H(3″), H(5″), H(6″))
CN	116.3 (H(4))	116.4	116.5 (H(4))	116.5 (H(4))

[a] The protons found to be involved in correlation are given in parentheses.
[b] The HMBC spectrum could not be recorded due to the low solubility of **7b**.
[c] δ_C NMe is 29.5.
[d] The signal cannot be isolated due to noise.
[f] The numbering of C atoms in the $C_6H_4NO_2$-*p* fragment.
[e] The numbering of C atoms in the C_6H_4R-*p* fragment.

passing from **7b** to **9b**. This altogether indicates that structural changes involve predominantly the pyridine fragment of the molecule.

To prove unambiguously the structures of compounds **7a** and **9a**, a powder X-ray diffraction study was performed for them (we were unable to prepare single crystals of an appropriate size) (Figs. 1 and 2).

A detailed description of the powder X-ray diffraction experiment, the solution and refinement of the molecular and crystal structures of **7a** and **9a**, and atom coordinates are reported in another publication.[17]

Methylation of compounds **7a,b** and **9a,b** with methyl iodide in the presence of potassium *tert*-butoxide gives rise to *N*-methyl derivatives **10a,b**, whose spectral characteristics are very close to those of **9a,b** (^{1}H and ^{13}C NMR, UV). However, the rate of methylation of **7a,b** (TLC) is much lower than that in the case of **9a,b**. In addition, TLC monitoring of the methylation of **7a,b** allows one to observe the intermediate formation of compounds **9a,b**. Naturally, the next stage of our work was an attempt to perform isomerization in the presence of potassium *tert*-butoxide. It was found that, whereas the **7**→**9** thermal transformation requires heating to 300 °C, isomerization in the presence of a strong base occurs at a much lower temperature to give products in high yields. This led to the conclusion that the formation of the intermediate anion greatly facilitates isomerization.

Thus, in all probability, treatment of carbolines **7a,b** with methyl iodide in the presence of Bu^{t}OK induces their rearrangement into isomers **9a,b** and only after that, methylation products **10a,b** are formed.

The **7**→**9** isomerization process can be interpreted rather reliably (Scheme 5). Apparently, a four-membered transition state is produced similar to that postulated for the Chapman thermal rearrangement.[15,16] It is clear that the "imino ester" rearrangement described in the study cited and the "amidine" rearrangement described here are somewhat different. This can be seen from the mere fact that in our case, the process is markedly facilitated upon the formation of anion **11**.

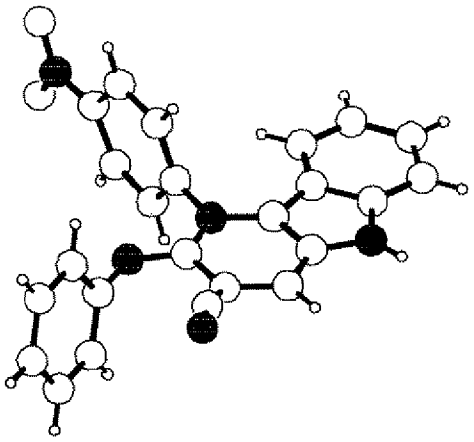


Fig. 1. Crystal structure of molecule **7a**.

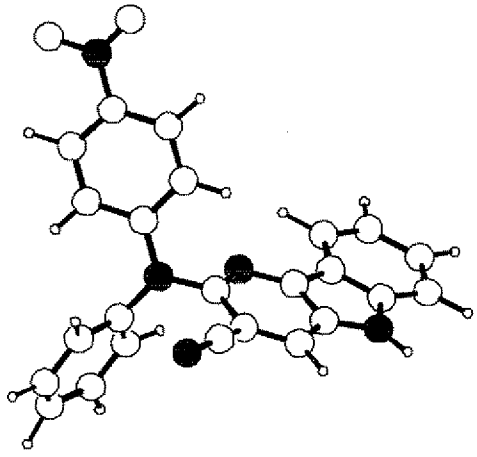
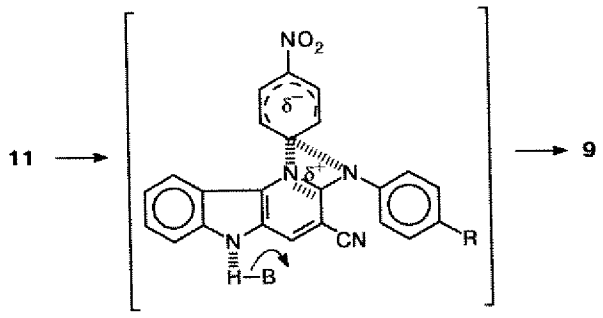


Fig. 2. Crystal structure of molecule **9a**.

Scheme 5



B — base.

To summarize, in this study, we have developed a new pathway to various pyrido[3,2-*b*]indole (δ-carboline) derivatives and have found a rearrangement of 1,2-diaryl-2-imino-δ-carbolines into 2-diarylamino-δ-carbolines.

Experimental

The IR spectra of compounds were recorded on Perkin—Elmer 457 instruments in mineral oil. Mass spectra (EI) were recorded on a Finnigan SSQ-710 mass spectrometer with direct sample injection into the ion source. ^{1}H NMR spectra were recorded on a Bruker AC-200 spectrometer; and two-dimensional HMBC NMR spectra were run on a Bruker DRX-500 instrument using standard procedures of the company. UV spectra were measured on a Perkin-Elmer Lambda 9 instrument. The reactions were monitored and the purity of compounds was checked on Silufol UV-254 plates in a 9 : 1 chloroform—methanol mixture (visualization under UV radiation) and in a 5 : 3 : 1 ethyl acetate—propan-2-ol—ammonia mixture (for compounds **4a,b**, **7a,b**, **8a,b**). X-ray diffraction measurements were carried out in a Guinier—Johansson cham-

ber. The structures of compounds **7a** and **9a** were solved by the systematic search method.[18]

Physicochemical characteristics and the yields of substances are presented in Table 2.

2-Chloro-3-cyano-2-dimethylamino-1-*p*-nitrophenyl-1*H*-pyrido[3,2-*b*]indole (4a). A suspension (3.3 g, 1 mmol) of δ-carbolin-2-one **1** [3] and triethylamine hydrochloride (1.4 g, 1 mmol) in 160 mL of $POCl_3$ was refluxed for 6 h. (After 1—1.5 h, the reaction mixture became homogeneous and subsequently a precipitate formed). The mixture was allowed to stand for 12 h at 20 °C and the precipitate was filtered off, washed with $POCl_3$ and water, and refluxed with 50—70 mL of acetone. The precipitate was filtered off, washed with acetone, and dried at 100 °C to give 2.86 g of salt **2** (or **3**) (m.p. > 300 °C).

Dimethylamine was passed for 2 h through a suspension of 1.2 g of salt **2** (or **3**) in 30 mL of CH_2Cl_2 with stirring and ice-water cooling. Then the reaction mixture was refluxed for 2 h and allowed to stand for 16 h at 20 °C. The dimethylamine hydrochloride precipitate was filtered off and the mother liquor was concentrated. The residue was triturated with water. The precipitate was separated, washed with water, and refluxed with propan-2-ol. The hot suspension was filtered to give 0.35 g of a substance, which was then refluxed for 5 min with 15 mL of concentrated HCl. The mixture was cooled and the precipitate was filtered off and dissolved in 100 mL of boiling water. The solution was filtered and combined with the acidic mother liquor, the mixture was decolorized by adding activated carbon, and then 11 mL of 40% NaOH was added. The resulting red precipitate was filtered off and washed with water, isopropyl alcohol, and ether to give 0.21 g of compound **4a**. ^{1}H NMR (DMSO-d_6) δ: 2.81 (both s, each 3 H, NMe_2); 6.12 (d, 1 H, H(9), J = 8.4 Hz); 6.73 (t, 1 H, H(8)); 7.36 (t, 1 H, H(7)); 7.65 (d, 1 H, H(6)); 8.92 (s, 1 H, H(4)); 8.66, 8.13 (AA′XX′, 4 H, $C_6H_4NO_2$).

3-Cyano-1-*p*-nitrophenyl-2-piperidino-1*H*-pyrido[3,2-*b*]indole (4b). Piperidine (0.3 mL, 3 mmol) was added with stirring and cooling to a suspension of salt **2** (or **3**) (0.2 g) in 10 mL of CH_2Cl_2. The red solution thus formed was stirred for 24 h at 20 °C. The resulting red precipitate was filtered off and washed with CH_2Cl_2 and acetone to give 0.08 g of compound **4b**. ^{1}H NMR (DMSO-d_6), δ: 0.80, 1.42, 3.17 (all br.s, 10 H, 5 piperidine CH_2); 6.18 (d, 1 H, H(9)); 6.74 (t, 1 H, H(8)); 7.36 (t, 1 H, H(7))); 7.65 (d, 1 H, H(6)); 8.92 (s, 1 H, H(4)); 8.12, 8.67 (AA′XX′, 4 H, $C_6H_4NO_2$).

3-Cyano-5-methyl-1-*p*-nitrophenyl-2-piperidino-5*H*-pyrido[3,2-*b*]indolium iodide (5). Methyl iodide (0.4 mL) was added to a suspension of carboline **4b** (0.34 g, 0.86 mmol) in 20 mL of benzene and the mixture was refluxed for 28 h. Portions of MeI (0.6 mL) were added every 7 h. The precipitate was filtered off and washed with benzene to give 0.42 g of iodide **5**. ^{1}H NMR (DMSO-d_6), δ: 1.22, 1.40, 3.20 (all br.m, 10 H, 5 piperidine CH_2); 4.20 (m, 3 H, NMe); 6.37 (d, 1 H, H(9)); 7.21 (t, 1 H, H(8)); 7.85 (t, 1 H, H(7)); 7.98 (d, 1 H, H(6)); 9.70 (s, 1 H, H(4)); 8.22, 8.76 (AA′XX′, 4 H, $C_6H_4NO_2$). IR, ν/cm^{-1}: 2220 (C≡N).

4-Acetonyl-3-cyano-5-methyl-1-*p*-nitrophenyl-2-piperidino-1,4-dihydropyrido[3,2-*b*]indole (6). A mixture of iodide **5** (0.27 g, 0.5 mmol), potassium carbonate (0.4 g, 2.8 mmol), and 15 mL of acetone was refluxed with stirring for 10 h. The inorganic salts were filtered off and washed with acetone. The mother liquor was concentrated and the residue was triturated with water. The precipitate was filtered off and washed with water and methanol to give 0.16 g of a solid material, which was refluxed with 15 mL of methanol. The insoluble precipitate was filtered off from the hot solution to give 0.08 g of compound **6**. Cooling of the methanolic mother liquor gave an additional 0.03 g of compound **6**. The overall yield of **6** was 0.11 g. ^{1}H NMR (DMSO-d_6), δ: 1.10—1.50 (both m, 6 H, 2 H(3), 2 H(5), 2 H(4) piperidine); 3.20 (br.m, 4 H, 2 H(2), 2 H(6) piperidine); 3.73 (m, 3 H, NMe); 2.1 (s, 3 H, C(4)—CH_2COMe); 2.83 (d, 2 H, C(4) $\underline{CH_2}$COMe, J = 6.1 Hz); 4.35 (t, 1 H, H(4)); 6.98 (d, 1 H, H(9)); 7.15 (t, 1 H, H(8)); 7.28 (t, 1 H, H(7)); 7.46 (d, 1 H, H(6)); 7.72, 8.34 (AA′XX′, 4 H, $C_6H_4NO_2$). IR, ν/cm^{-1}: 2180 (C≡N), 1710 (C=O).

3-Cyano-1-*p*-nitrophenyl-2-phenylimino-1,2-dihydro-5*H*-pyrido[3,2-*b*]indole (7a) and its hydrochloride (8a). Aniline (2.22 mL, 24 mmol) was added with stirring at 20 °C to a suspension of salt **2** (or **3**) (1.45 g) in 15 mL of DMF. The resulting red solution was stirred for 5—6 h and allowed to stand for 16 h. The resulting precipitate was filtered off and washed with DMF and ether to give 0.8 g of bright yellow hydrochloride **8a**. The mother liquor was concentrated, water (30 mL) was added to the oily residue, and the mixture was stirred and acidified with ~1 mL of concentrated HCl (to pH 2). The red precipitate was filtered off, washed with water, and dried at 100 °C to give 0.94 g of a mixture of compound **7a** and its hydrochloride **8a**. Methanol (20 mL) and several drops of 40% NaOH were added to this mixture, the mixture was heated to boiling with stirring and cooled, and the precipitate was filtered off, washed with methanol, and dried to give 0.3 g of compound **7a**.

2-*p*-Chlorophenylimino-3-cyano-1-*p*-nitrophenyl-1,2-dihydro-5*H*-pyrido[3,2-*b*]indole (7b) was prepared similarly to compound **7a** from salt **2** (or **3**) (1 g), *p*-chloroaniline (1.33 g, 1.04 mmol) in 15 mL of DMF. After keeping (16 h), the reaction solution was filtered to remove a slight amount of a resinous precipitate and concentrated. The subsequent workup, the same as described for compound **7a**, gave 0.8 g of compound **7b**.

Preparation of hydrochlorides 8a,b from bases 7a,b. δ-Carboline **7a** or **7b** (0.36 mmol) was dissolved in 10 mL of acetone. The solution was filtered, and HCl-saturated ether was added with cooling and stirring until the red color changed to yellow. After 2 h, the resulting precipitate (colored yellow) was filtered off and washed with acetone to give chlorides **8a** or **8b** in ~60% yield. The melting point of a mixed sample consisting of chloride **8a** and the salt isolated upon the reaction of salt **2** (or **3**) with aniline (see above) was undepressed. ^{1}H NMR (hydrochloride **8a**) (DMSO-d_6), δ: 7.20—7.50 (m, 5 H, C_6H_5); 6.08 (d, 1 H, H(9)); 7.05 (t, 1 H, H(8)); 7.63 (t, 1 H, H(7)); 7.78 (d, 1 H, H(6)); 9.18 (s, 1 H, H(4)); 8.27, 8.73 (AA′XX′, 4 H, $C_6H_4NO_2$); 9.64 (br.s, 1 H, N(2)H); 13.37 (br.s, 1 H, N(5)H). ^{1}H NMR (hydrochloride **8b**) (DMSO-d_6), δ: 7.38 (AA′XX′, 4 H, C_6H_4Cl); 6.09 (d, 1 H, H(9)); 7.05 (t, 1 H, H(8)); 7.63 (t, 1 H, H(7)); 7.77 (d, 1 H, H(6)); 9.16 (s, 1 H, H(4)); 8.24, 8.71 (AA′XX′, 4 H, $C_6H_4NO_2$); 9.56 (br.s, 1 H, N^+H); 12.13 (br.s, 1 H, N(5)H).

3-Cyano-2-*p*-nitrophenyl(phenyl)amino-5*H*-pyrido[3,2-*b*]indole (9a). Method *A*. 2-Phenylimino-δ-carboline **7a** (red) (0.2 g, 0.49 mmol) was placed in a bath with Wood's alloy heated to 300 °C and then heated to 330 °C until the compound completely melted (2—3 min). Column chromatography on SiO_2 (chloroform as the eluent) gave 0.14 g of compound **9a** (colored yellow).

Method *B*. Potassium *tert*-butoxide (0.02 g, 0.18 mmol) was added to a solution of 2-phenylimino-δ-carboline **7a** (0.05 g, 0.12 mmol) in 3 mL of DMF, the mixture was refluxed for 5 min, and DMF was evaporated. Water (5—7 mL) and concentrated HCl (0.02 mL) were added to the residue. The precipitate was filtered off and washed with water and methanol

to give 0.03 g of compound **9a**. The melting point of a mixed sample of this product with the compound prepared by method *A* was undepressed.

Method *C*. 2-Phenylimino-δ-carboline hydrochloride **8a** (0.8 g, 1.8 mmol) was dissolved with heating in 20 mL of DMF, Bu^{t}OK (0.8 g, 7.3 mmol) was added, and the mixture was refluxed for 25—30 min and worked-up by the procedure described above (*B*) to give 0.6 g of compound **9a**. The melting point of a mixed sample of this product with the compound prepared by method *A* was undepressed.

3-Cyano-2-*p*-nitrophenyl(*p*-chlorophenyl)amino-5*H*-pyrido[3,2-*b*]indole (9b) was prepared from 2-*p*-chlorophenylimino-δ-carboline **7b** (0.13 g, 0.3 mmol), similarly to method *A* described for compound **9a**, but with a bath temperature of 200—260 °C. The residue was purified by recrystallization from methanol to give 0.08 g of compound **9b**.

3-Cyano-5-methyl-2-*p*-nitrophenyl(phenyl)aminopyrido[3,2-*b*]indole (10a). Method *A*. Potassium *tert*-butoxide (0.1 g, 0.89 mmol) was added to a red-colored solution of 2-phenylimino-δ-carboline (0.3 g, 0.74 mmol) **7a** in 10 mL of DMF, the mixture was refluxed for 3—5 min, and ~5—8 mL of a mixture of DMF with Bu^{t}OH was distilled off. Fresh DMF (8 mL) and MeI (2 mL) were added, and the mixture was allowed to stand for 24 h at 20 °C. The KI precipitate was filtered off, DMF was evaporated, and the residue was mixed with water. The resulting precipitate was filtered off and washed with water and isopropyl alcohol on the filter with stirring to give 0.18 g of compound **10a**. ^{1}H NMR (DMSO-d_6), δ: 4.00 (s, 3 H, NMe); 6.89, 8.11 (AA′XX′, 4 H, $C_6H_4NO_2$); 7.25—7.38 (m, 4 H, H(2′), H(6′), H(4′), H(8)); 7.47 (t, 2 H, H(3′), H(5′)); 7.77 (m, 2 H, H(6), H(7)); 8.13 (d, 1 H, H(9)); 8.83 (s, 1 H, H(4)).

Method *B*. The reaction of δ-carboline **9a** (0.11 g, 0.27 mmol), Bu^{t}OK (0.04 g, 0.33 mmol), DMF (5 mL), and MeI (1 mL) as described in method *A* gave 0.1 g of compound **10a**. The melting point of a mixed sample of this product with the compound prepared from **7a** was undepressed. The ^{1}H NMR spectra of the samples were identical.

3-Cyano-5-methyl-2-*p*-chlorophenyl(*p*-nitrophenyl)amino-3-cyanopyrido[3,2-*b*]indole (10b). Method *A*. The transformation of δ-carboline **7b** (0.18 g, 0.41 mmol) gave 0.04 g of compound **10b** (red-colored), which was purified by column chromatography on SiO_2 (chloroform as the eluent). The synthesis was similar to the synthesis of **10a** (with the difference that the reaction mixture was allowed to stand for 48 h).

Method *B*. The transformation of δ-carboline **9b** (0.19 g, 0.43 mmol) gave 0.16 g of **10b**. The synthesis was similar to the synthesis of **10a** by method *B* (with the difference that the time of keeping the reaction mixture was 3 h). The melting point of a mixed sample of this product with the compound prepared by method *A* was undepressed. The ^{1}H NMR spectra of the samples were identical. ^{1}H NMR (DMSO-d_6), δ: 3.99 (s, 3 H, NMe); 7.27—7.48 (AA′XX′, 4 H, C_6H_4Cl); 8.10 (d, 1 H, H(9)); 7.31 (t, 1 H, H(8)); 7.70 (t, 1 H, H(7)); 7.77 (d, 1 H, H(6)); 8.82 (s, 1 H, H(4)); 6.93, 8.11 (AA′XX′, 4 H, $C_6H_4NO_2$).

The authors are grateful to A. I. Bokanov for assistance in determining the structures of the rearranged products.

References

1. R. A. Abramovitch and I. D. Spenser, *Adv. Heterocycl. Chem.*, 1964, **3**, 79.
2. M. D. Mashkovskii, *Lekarstvennye sredstva* [*Medicinals*], Novaya volna, Moscow, 2000, **I**, 279, 278, 97 (in Russian).
3. S. Yu. Ryabova, L. M. Alekseeva, and V. G. Granik, *Khimiya Geterotsikl. Soedin.*, 2000, 362 [*Chem. Heterocycl. Compd.*, 2000 (Engl. Transl.)]
4. W. Kantlehner, in *Iminium Salts in Organic Chemistry*, Ed. H. Bohme and H. G. VieHe, J. Wiley and Sons, New York—London—Sydney—Toronto, 1979, Part 2, 6.
5. H. Bredereck and K. Bredereck, *Chem. Ber.*, 1961, **94**, 2278.
6. H. Bredereck, R. Gompper, K. Klemm, and H. Rempfer, *Chem. Ber.*, 1959, **92**, 837.
7. K. Bredereck, F. Effenberger, and H. Botsch, *Chem. Ber.*, 1964, **97**, 3397.
8. K. Bredereck and S. Humburger, *Chem. Ber.*, 1966, **99**, 3227.
9. I. M. Ovcharova and E. S. Golovchinskaya, *Zh. Obshch. Khim.*, 1964, **34**, 2472 [Chem. Abstrs., 1964, **61**: 9497d].
10. V. G. Granik, V. F. Knyazeva, I. V. Persianova, N. P. Solov′eva, and R. G. Glushkov, *Khimiya Geterotsikl. Soedin.*, 1982, 1095 [*Chem. Heterocycl. Compd.*, 1982, **18**(8), 838 (Engl. Transl.)].
11. Z. Arnold and A. Holy, *Collection Czech, Chem. Commun.*, 1962, **27**, 2886.
12. H. H. Bosshard and H. Zollinger, *Helv. Chim. Acta*, 1959, **42**, 1659.
13. S. Yu. Ryabova, L. M. Alekseeva, and V. G. Granik, *Mendeleev Commun.*, 1995, 107.
14. S. Yu. Ryabova, L. M. Alekseeva, and V. G. Granik, *Khim.-Farm. Zhurn.*, 1996, **30**(9), 29 [*Pharm. Chem. J.*, 1996, **30**(9), 579 (Engl. Transl.)].
15. A. W. Chapman, *J. Chem. Soc.*, 1925, **127**, 1992.
16. O. H. Wheeler, F. Roman, and O. J. Rosado, *J. Org. Chem.*, 1969, **34**, 966.
17. V. V. Chernyshev, V. A. Tafeenko, S. Yu. Ryabova, E. J. Sonneveld, and H. Schenk, *Acta Crystallogr., Sec. C*, 2001, **C57**, 982.
18. V. V. Chernyshev and H. Schenk, *Z. Kristallogr.*, 1998, **213**, 1.

Received April 11, 2001